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Use of α-MSH and/or EPO separately or in combination
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Use of α-MSH and/or EPO separately or in combination for the prevention or treatment of heart conditions.

The present invention relates to a method for treating or preventing a condition related to the tissue of the heart of a mammal. The method comprises administration of an effective dose of an α-MSH and/or of an α-MSH equivalent and EPO and/or an EPO equivalent to an individual in need thereof. In a preferred embodiment, the invention relates to a combination of α-MSH and/or of an α-MSH equivalent with an EPO and/or an EPO equivalent to be administered to the individual in need thereof for treatment or prevention of a heart condition of the individual. In a further aspect the invention relates to use of α-MSH and/or of an α-MSH equivalent and EPO and/or an EPO equivalent for the preparation of a medicament together with a pharmaceutically acceptable carrier. In a still further aspect, the invention relates to a medicament comprising a combination of α-MSH and/or of an α-MSH equivalent and EPO and/or an EPO equivalent.

According to the present invention it has surprisingly been found that treatment with either α-MSH, high dose rh-EPO, or combined treatment with α-MSH and low dose rh-EPO significantly reduced infarction size evaluated two hours after reperfusion of the ischemic myocardium.

In another set-up of animals, 5 out of 11 vehicle treated rats and 2 out of 8 rats treated with low dose rh-EPO died during the three following days. Rats treated with α-MSH, high dose rh-EPO, or combined treatment with α-MSH and low dose rh-EPO where all alive three days after sixty minutes myocardial ischemia.

On day three, the surviving vehicle treated animals had significantly increased LVEDP compared to Sham-operated controls. +dP/dT was significantly decreased and -dP/dT increased in the vehicle treated animals. Low dose rh-EPO did not prevent the impairment of cardiac function found in the vehicle treated animals. However, the impairment of cardiac function was significantly blunted in rats treated with high dose rh-EPO, α-MSH or combined treatment with low dose rh-EPO and α-MSH.

D tail d description of th Inv nti n

In one embodiment, the present invention refers to a method for treatment or prevention of a condition related to the tissue of the heart of a mammal. The method comprises administration of an effective dose of an α-MSH and/or of an α-MSH equivalent or administration of an EPO and/or an EPO equivalent to a patient in need thereof. In an improved embodiment, the invention relates to a combination of α-MSH and/or of an α-MSH equivalent with an EPO and/or an EPO equivalent to be administered to the individual in need thereof for treatment or prevention of a heart condition of the individual.

Any tissue related to the heart may be subject of the method according to the invention. Accordingly, the condition to be treated may be located or related to any tissue selected from the endocardial tissue, the atrial myocardium; ventricular myocardium; of the heart including the sinoatrial (SA) node and the atriventricular (AV) node; and the pericardium.

In one important aspect of the invention, the condition is due to or caused by ischemia of the tissue such as in arterial stenosis or any other coronary artery disease. The ishemia may be acute or chronic depending on the severity of the disease and, furthermore, the condition may be reversible or irreversible. An example of a reversible condition may be due to fall in the blood pressure during surgery or other intervention in the blood perfusion of the heart. Accordingly, the condition may be any decrease in systemic blood flow to the heart, such as hypotension.

The method of the invention may be of special benefit in relation to conditions caused by or associated with heart transplantation, including prevention of graft versus host reaction. In such conditions, the entire organ is extremely sensitive to all alterations with respect to nutrition, metabolism, perfusion etc., and the treatment according to the present invention is believed to stabilise the condition and make the heart tissue more resistant to any situation stressing the function of the organ. The method according to the present invention also encompasses administration to the heart transplant during transport to the recipient, including addition of the pharmaceuticals to the transportation medium.

One of the most common heart conditions is intermittent angina or chest pain wherein the treatment according to the invention may be of special interest. Conditions relating to

angina includes unstable angina, stable angina, Prinzmetal's variant angina, and Syndrome X.

In a further aspect, the prevention and treatment may be utilised in situations caused by pericarditis, myocardiel infarction, myocardial ishaemia, myocarditis, myxodemia, and endocarditis.

Many heart conditions are associated with cardial arrhythmia. Either as the primary disease or secondary to another condition of the individual. Examples of miscellaneous causes of arrhythmia include acute infections particularly those affecting the lungs, pulmonary embolism, hypotension, shock, anoxaemia or anaemia which can precipitate myocardial ischaemia and thus cause arrhythmia. The arrhythmia will aggravate the circulatory disturbance and thereby set up a vicious, self-perpetuating cycle.

It is believed that the treatment according to the present invention will increase the threshold for development of arrhythmia thus preventing the development of the arrhythmia. The effect may by directly on the conduction system or indirectly by acting on a condition tricking or being the cause of the arrhythmia.

Antiarrhythmic therepy performed with the aim of suppressing an arrhythmia is always associated with a risk of creating new arrrhythmias. The arrhythmias may occur as a toxic reaction due to an overdose of the drug. However, particularly during treatment with the group of drugs known as Class IA drugs, arrhythmias can occur as a non dosage-dependent side effect - an idiosyncratic reaction - developing at drug concentrations well within the therapeutic range. According to a further embodiment, the condition may be causes by one or more antiarrhytmic drugs including, digitalis, quinidine, disopyramide, adenosin, aprindine, flecainide, amiodarone, sotalol, meciletine, beta blocking agents, and verapamil.

In a syndrom or an arrhythmia which can be alleviated according to the present method may be either primary or secondary and may be selected from ventricular or supra ventricular tachyarrhythmias, atrioventricular block, sinus node disease, Wolff-Parkinson-White syndrome, Lenégres disease, Lev's disease any syndrome involving an abnormal myocardial connection between atrium and ventricle.

In a still further aspect, the condition may be associated with a chemical trauma including toxic substances and drugs. Such drugs include tricyclic antidepressants, lithium salts, prenylamine, phenothizine derivatives, chemopreventive drugs including adriamycin. Also physical traumas including electromagnetic radiation may cause damages which can be alleviated with the method of the present invention.

The condition involved in the heart according to the present invention may further include connective tissue disease such as scleroderma, systemic lupus erythematosus or by neuromyopathic disorders such as progressive muscular dystrophy of Duchenne's type, Friedreich's ataxia, and myotonic dystrophy.

Many infections associated with the heart may have an influence on the heart tissue and disturb the normal function resulting in decreased performance. Such infections include infections by protozoa, virus, bacteria, fungus and including AIDS virus, bacterial septicemia, systemic fungal infections, Rickettsial diseases, toxic shock syndrome, infectious mononucleosis, chlamydia thrachomatis, chlamydia psittaci, cytomegalovirus infection, cambylobacter, salmonella, influenza, poliomyelitis, toxoplasmosis, Lassa Fever, Yellow Fever, billharziose, colibacteria, enterococcer, preteus, klebsiella, pseudomonas, staphylococcus aureus, staphylococcus epidermidis, candida albicans, tuberculosis, mumps, infectious mononucleusis, hepatitis and Coxackie virus

In a further embodiment, the condition may be caused by a cancer or a by premalignant disorder having an impact of the heart, including acute leukemia, chronic myelocytic leukemia, chronic lymphocytic leukemia, Hodgkin's disease, lymphosarcoma, myeloma, metastasing carcinoma of any origin.

Furthermore, the condition may be caused by any disease selected from diabetis mellitus, conditions with increased fasting levels of LDL-Cholesterol, conditions with combined increased fasting levels of LDL-Cholesterol and tryglycerid, conditions with increased fasting levels of triglycerid, , conditions with increased fasting levels of HDL-Cholesterol, retroperitoneal fibrosis, lupus erythematosus, polyarteritis nodosa, sclerodermia, polymyositis, dermatomyositis, rheumatoid arthritis, anaphylaxis, serum sickness, hemolytic anaemia, and allergic agranulocytosis.

According to the present invention, the tissue of the heart which may be affected also includes one or more cell types present in the heart and may be selected from macrophages, the reticulo endothelial system monocytes, neutrophil granulocytes, eosinophil granulocytes, basophil granulocytes, T-cells, B-cells, mast cells, and dendritic cells. Especially, the T-cells, B-cells, and mast cells may be of certain interest in this respect.

Other conditions which may be alleviated by use of the present method are the effect of electrolyte derangement on the heart as well as the derangement itself, including abnormalities in the relative concentrations of individual ions one to another. Such condition includes an abnormal serum concentration of one or more of the group comprising potassium, calcium, sodium, and magnesium.

In a further aspect of the invention, the condition may be characterised by one or more abnormalities as measured by electrocardiography (ECG). The abnormality on the ECG may relate to an alteration selected from one or more changes in the configuration selected from the P wave, the ST segment, the T wave, the QRS complex, the Q wave, the delta wave, and the U wave.

A preferred aspect of the invention relates to the preventing treatment wherein the dose of α-MSH and/or of an α-MSH equivalent or a EPO and/or an EPO equivalent or a combination thereof is administered profylactically for preventing a progress of the condition or of any symptom of the condition. The preventive treatment may be an ongoing treatment during e.g. surgery or for the prevention of heart attacks in a patient suffering from coronary stenosis. The preventive treatment may also be for a limited period. The skilled person will be able to evaluate the specific treatment schedule based on the actual situation. In a preferred embodiment, the treatment or prevention according to the present invention relates to reducing the infarction size upon ischaemia of the coronary arteries. Such infarction size may be reduced by 20%, such as at least 30%, preferably by at least 50% compared to the untreated individual as will appear from the example herein.

Accordingly, the dose of α-MSH and/or of an α-MSH equivalent or a EPO and/or an EPO equivalent or a combination thereof is administered profylactically for prevention of the establishment of the condition or of any symptom of the condition.

The dose of α-MSH and/or of an α-MSH equivalent or a EPO and/or an EPO equivalent or the combination thereof may be administered as a single dosage, regular or continued administration, or as a sequential administration.

The administration may be parenteral administration, including intraperitoneal administration, intrathecal administration, systemic administration, local administration including use of drug target systems and implants, topical administration, transmucosal administration and transdermal administration and oral administration.

Accordingly, the administration includes systemic administration; injection into tissue or into a body cavity including joints; implantation into tissue or into a body cavity; topical application to the skin or to any gastrointestinal surface, or to a mucosal surface including the lining of body cavities.

The α-MSH equivalent according to the present invention is preferably a substance acting on an α-MSH receptor and/or on the melanocortin receptor such as subtypes 1 to 5 (MC-receptors 1-5).

In a further important aspect, the α-MSH equivalent is a polypeptide having at least 3 amino acids including the following sequence Lys-Pro-Val, such as Gly-Lys-Pro-Val, or the following sequence His-Phe-Arg,

A very important aspect of the present invention is the beneficial effect of the combination of the use of α-MSH or α-MSH equivalent with EPO and/or an EPO equivalent. Especially, as the combination may have an additive effect on the condition to be treated. An additive effect may be measured as an effect increasing any of the effects of the individual drugs used in the same dosage. However, it is believed that the combination in most circumstances may have a synergistic effect. A synergistic effect may be measured as an effect increasing the sum of the individual effect of each of the individual drugs used in the same dosage. A synergistic effect may also include the situation where an effect equal to the sum of effects by the individual treatments is obtained with use minor doses of the individual drugs when used in combination.

In a still further aspect, th present invention relates to the use of α-MSH and/or a equivalent of α-MSH or of a EPO and/or an EPO equivalent or a combination of α-MSH and/or of an α-MSH equivalent with a EPO and/or an EPO equivalent for the preparation of a medicament for treatment or prevention of any of the conditions disclosed herein.

Accordingly, the preparation of a medicament includes medicaments for injection or systemic administration, such as a medicament in a form suitable for injection or systemic administration, e.g. a solution or a suspension.

The medicament may be for implantation including implants or other devices wherein the medicament is incorporated into a coating of a medico technical device or is incorporated into the material of the device itself, including artificial heart valves and stents. The active ingredients may be incorporated into or onto the device by use of a suitable polymer.

Furthermore, the medicament may be prepared for topical application in the form of a powder, paste, ointment, lotion, gel, cream, emulsion, solution, suspension, spray, aerosol, sponge, strip, plaster, or pad. Furthermore, the medicament may be prepared for oral administration in the form of tablets, sustained release tablets, or resoritablets. When for topical application, the medicament may be prepared in the form of a preparation suitable for application on mucosa e.g. a suppository, a tampon, a suspension for irrigation, a tablet or troche, a cream or gel or ointment; or for application on urethral mucosa, a bladder insert, or an implant.

The α-MSH and/or α-MSH equivalent or EPO and/or an EPO equivalent or the combination thereof may be present in the medicament in an amount of 0.001-99%, typically 0.01-75%, more typically 0.1-20%, especially 1-15 such as 1-10% by weight of the medicament.

The dose depends on the conditions to be treated. The individual drugs may be used in the doses known in the art. However, according to the present invention minor doses will generally be sufficient. With respect to the use of the combination, the EPO may very often be effective in rather small doses. The necessary dose of EPO in the combination may be such a dose which, when used alone, would not have any significant effect on the condition.

In a still further aspect, the present invention relates to a pharmaceutical composition comprising a combination of α-MSH or and/or α-MSH equivalent and EPO and/or an EPO equivalent with a pharmaceutically acceptable carrier. In an interesting aspect, the α-MSH or α-MSH equivalent and EPO and/or an EPO equivalent is a physical entity.

The pharmaceutical compositions according to the present invention may be prepared by use of conventional techniques known in the art and with conventional pharmaceutical carriers. Furthermore, the pharmaceutical composition may be in any form suitable for any of the uses as described herein.

In a preferred embodiment, the α-MSH, α-MSH equivalent, EPO and EPO equivalent is in the form of the recombinant produced proteins.

Example 1

Treatment with alfa-MSH or epoetin separately or combined prevents death and cardiac dysfunction induced by myocardial Ischemia

Introduction

Ischemia induced by reduced/complete arrest in arterial blood supply induces multiple tissue reactions including neutrofil accumulation, other inflammatory responses, and cell death. Identification of compounds that could inhibit or prevent (either completely or partially) many of the cell/tissue/organ impairments or destructions occurring as a result of ischemia/inflammation would be of great benefit.

Acute myocardial infarction (AMI) is one of the most common causes of death in the developed countries. The incidence of AMI in a country as Denmark with 5,000,000 citizens, is 19,000. The pre-hospital mortality is 15%, which means that approximately 16,000 patients are hospitalized with AMI every year. The acute mortality among these patients is 20%. The one-year mortality among patients who leave hospital is 5-10%.

AMI almost always occurs in patients with coronary atheroma because of sudden coronary thrombosis. Today, fibrinolytic therapy and primary percutaneous transluminal

coronary angioplasty (PTCA) are standard treatments and can achieve early reperfusion in 50-70% of patients (spontaneous reperfusion rate is less than 30%). However, early intervention is necessary in order to reduce the ischemic damages and patients with AMI still develop irreversible ischemic myocardial damages with the development of impaired myocardial function. The long term-prognosis after AMI has shown to be directly correlated to left-ventricular function evaluated through eccocardiographic measurement of left ventricular ejection fraction. Identification of compounds that could inhibit or prevent (either completely or partially) many of the cell/tissue/organ impairments or destructions occurring as a result of ischemia in the infarcted and reperfused myocardium would be attractive tools in inter alia reducing the irreversible damages that eventually result in impaired myocardial function after AMI.

The potential beneficial role of α-MSH, rh-EPO or combined treatment with both compounds in AMI has never been established. Therefore, we have performed a series of experiments in a model of coronary ischemia/reperfusion in rats. The role of i.v. treatment with α-MSH (200 µg/day/kg b.w.), rh-EPO in two different doses (200 and 1000 U/day/kg b.w.) and, finally, the role of combined treatment with α-MSH (200 µg/day/kg b.w.) and low dose rh-EPO (200 U/day/kg b.w.) on myocardial remodeling and cardiac performance after sixty minutes ischemia were investigated.

Methods

Materials

Barrier-bred and specific pathogen-free female Wistar rats (250 g) were obtained from the Department of Experimental Medicine, Panum Institute, University of Copenhagen, Denmark. The animals were housed in a temperature (22-24°C) and moisture (40-70%) controlled room with a 12-hour light-dark cycle (light on from 6:00 A.M. to 6:00 P.M.). All animals were given free access to tap water and a pelleted rat diet containing approximately 140 mmol/kg of sodium, 275 mmol/kg potassium and 23 % protein (Altromin catalogue no. 1310, Altromin International, Lage, Germany).

Animal preparation

Rats were anaesthetized in an inhalation chamber with 4% isoflurane in O_2. After insertion of an endotracheal tube, the animal was artificially ventilated with1.0 % isoflurane in O_2 using of Hugo Basile Rodent ventilator. Tidal volume was 8-10 ml/kg b.w. and respiratory

rate 75 min^{-1} which maintained arterial pH between 7.35 and 7.45. During surgery the animal was placed on a heated table that maintained rectal temperatur at 37-38°C. Permanent medical grade Tygon catheters were implanted into the inferior caval vein and into the abdominal aorta via the femoral vein and artery. Standard ECG (second lead) was measured using a Hugo Sachs ECG Coupler and collected on line at 4,000 Hz in PowerLab. After parasternal thoracotomy and opening of the pericardium, the left anterior descending coronary artery (LAD) was localized visually. Rats where the LAD could not be visualized were used as sham-operated control rats. An atraumatic 6-0 silk suture with an occluder that allowed reopening of the ligature, was placed around the LAD between the pulmonary trunk and the lower right end of the left auricle. After 10 minutes, the left anterior descending coronary artery (LAD) was occluded. Successful occluding was confirmed by alterations in ECG (ST-segment elevation and increase in R-wave amplitude) and by fall in MAP. Reperfusion was made after 60 minutes by opening the occluder. Control rats were sham-operated.

Experimental groups:

The rats were subjected to one of the following i.v treatments:

Vehicle: 0.5 ml 150 mM NaCl once daily.

α-MSH: 200 µg α-melanocyte stimulating hormone/kg b.w. in 0.5 ml 150 mM NaCl once daily.

rh-EPO-200: 200 I.U. epoitin alfa/kg b.w. in 0.5 ml 150 mM NaCl once daily.

rh-EPO-1000: 1000 I.U. epoitin alfa/kg b.w. in 0.5 ml 150 mM NaCl once daily.

α-MSH+rh-EPO: 200 µg α-MSH and 200 I.U. EPO/kg b.w. in 0.5 ml 150 mM NaCl once daily.

Control: Sham operated rats treated with vehicle (0.5 ml 150 mM NaCl) once daily.

The first dose was given after 30 minutes ischemia.

Protocol 1: Determination of the size of the ischemic and necrotic myocardium.

The rats were kept anaesthetized after the ischemia/reperfusion and re-occluding of the LAD was performed after two hours reperfusion. During this period, ECG and MAP were measured continuously. Then Evans Blue dye (1 ml; 2% w/v) was administered i.v. to determine the size of the ischemic area. The heart was removed and cut into horizontal slices to determine the size of the ischemic area and to separate the ischemic myocardium from the non-ischemic myocardium. The ischemic area was isolated and

incubat d in a 0.5% triphenyltetrazolium chloride solution for 10 minutes at 37°C. The size of the necrotic tissue was then measured gravimetrically. N=6 in all groups.

Protocol 2: Measurement of hemodynamic dysfunction three days after ischemia/reperfusion.

After ischemia/reperfusion and initial treatment with vehicle, α-MSH, rh-EPO or α-MSH+EPO, the rats were placed in separate cages and were given free access to tap water and standard rat diet. To relieve postoperative pain, rats were treated with buprenorfin, 0.2 mg/kg b.w. i.p. twice daily for two days. Three days after ischemia/repserfusion the rats were anaesthetized with isoflurane in O_2. The concentration of isoflurane was adjusted to maintain after-load during anaesthesia, i.e MAP was stabilized at 95-100 mmHg. A 2F Millar microtip catheter was inserted into the left ventricle via the right carotic artery for measurement of left ventricular end diastolic pressure (LVEDP), and positive and negative dP/dT. Standard ECG (second lead) and MAP were measured throughout. The development of Q-waves was used as a sign of transmural infarction. N=6 in all groups, except in the Vehicle and the rh-EPO-200 groups, where the number of animals due to sudden death during the 3 days study period were 11 and 8 respectively.

Statistics

Data is presented as mean ± S.E.. Within-group comparisons were analyzed with Student's paired *t* test. Between-group comparisons were performed by one way analysis of variance followed by Fishers Least Significant Difference test. Differences were considered significant at the 0.05 level.

Results

Mortalility and Infaction size

All animals presented in study protocol 1 survived the two hours reperfusion period. In study protocol 2, the rats were followed for three days and during this period the mortality in the vehicle treated group was 45% (5 out of 11 animals) and 25% in the rats treated with low dose rh-EPO (2 out of 8 animals). All animals survived in the other groups, i.e. high dose rh-EPO treatment, α-MSH treatment; combined treatment with low dose rh-EPO and α-MSH, and in the sham-operated controls.

The mean area of risk was similar in all ischemia/reperfusion groups when the hearts were examined two days after reperfusion (figure 1). Vehicle treated rats had an infarct size of 67±7% of the area of risk. Low dose rh-EPO did not significantly reduce the size of the infarcted part of the area of risk. However, high dose rh-EPO as well as α-MSH significantly reduced infarction size. High dose Rh-EPO reduced the infarction size by 65% and α-MSH reduced the infarction size by 58% compared to the vehicle treated animals. Combined treatment with low dose rh-EPO and α-MSH reduced the size of the infarction size by 75%. The sham-operated time-control animals had no infarction (data not shown).

Changes in ECG

Baseline hemodynamics and ECG were similar in all groups (data not shown). Ischemia induced ST-elevation (and hypotension) in all animals. Sham-operation caused no changes in ECG (or MAP).

The surviving rats treated with vehicle and low dose rh-EPO developed coronary Q-waves when examined three days after ischemia/reperfusion. This sign of transmural myocardial infarction was lagging in rats treated with high dose rh-EPO, α-MSH and combined treatment with low dose rh-EPO and α-MSH.

Cardiac function three days after ischemia/reperfusion

At day three, the surviving vehicle treated animals had significantly increased LVEDP compared to Sham-operated time-controls (figure 2). +dP/dT was significantly decreased and -dP/dT increased in the vehicle treated animals. Low dose rh-EPO did not prevent the impairment in cardiac function found in the vehicle treated animals. However, the impairment in cardiac function was significantly blunted in rats treated with high dose rh-EPO, α-MSH or combined treatment with low dose rh-EPO and α-MSH.

Figure legends

Figure 1

Myocardial ischemia was induced by sixty minutes occlusion of the left anterior decending artery in isoflurane anesthetised rats. After two hours reperfusion, the artery was reoccluded, evans blue injected i.v and the non-coloured area repr sented the occluded

area (ar a of risk) (A). The area of risk (the ischemic area) was th n isolated and incubated in a 0.5% triphenyltetrazolium chloride solution for 10 minutes at 37°C in order to quantitate the nechrotic part of the area of risk (B).
*: P<0.05 vs. Vehicle.

Figure 2
Measurement of left ventricular end diastolic pressure (LVEDP) (A), and positive (B) and negative (C) dP/dT in isoflurane anaesthetised rats three days after sixty minutes occlusion of the left anterior descending artery. *: P<0.05 vs. Vehicle.

Claims

1. A method for treating or preventing a condition in the tissue of the heart of a mammal comprising administration of an effective dose of α-MSH and/or of an α-MSH equivalent or a EPO and/or an EPO equivalent or a combination of α-MSH and/or of an α-MSH equivalent with a EPO and/or an EPO equivalent to the individual in need thereof.

2. The method according to claim 1 wherein the tissue is selected from atrial myocardium; ventricular myocardium; the conduction system of the heart including the sinoatrial (SA) node and the atriventricular (AV) node; and the pericardium.

3. The method according to any of the preceding claims wherein the condition is caused by ischemia of the tissue.

4. The method according to claim 3 wherein the ischemia of the tissue is acute or chronic.

5. The method according to any of the preceding claims wherein the condition is reversible or irreversible.

6. The method according to any of the preceding claims wherein the condition is caused by coronary artery disease such as stenosis.

7. The method according to any of claims 1-5 wherein the condition is caus d by or associated with heart transplantation, including prevention of graft versus host reaction.

8. The method according to any of claims 1-5 wherein the condition is selected from unstable angina, stable angina, Prinzmetal's variant angina, and Syndrome X

9. The method according to any of the preceding claims wherein the condition is caused by pericarditis, myocardiel infarction, myocardial ishaemia, myocarditis, myxodemia, endocarditis.

10. The method according to any of the claims 1-5 wherein the condition is associated with cardial arrhytmia.

11. The method according to any of claims 1-5 wherein the condition is causes by one or more antiarrhytmic drugs including, digitalis, quinidine, disopyramide, adenosin, aprindine, flecainide, amiodarone, sotalol, meciletine, beta blocking agents, and verapamil.

12. The method according to any of the claims 1-5 wherein the condition is caused by connective tissue disease such as scleroderma, systemic lupus erythematosus or by neuromyopathic disorders such as progressive muscular dystrophy of Duchenne's type, Friedreich's ataxia, and myotonic dystrophy.

13. The method according to any of claims 1-5 wherein the condition is caused by decrease in systemic blood flow to the heart, such as hypotension.

14. The method according to any of claims 1-5 wherein the condition is caused by electrolyte derangement including abnormalities in the relative concentrations of individual ions one to another.

15. The method according to claim 14 wherein the condition is caused by an abnormal serum concentration of one or more of the group comprising potassium, calcium, sodium, and magnesium.

16. The method according to any of claims 1-5 wherein the condition is caused by or associated with a chemical trauma including toxic substances and drugs such as tricyclic

antidepressants, lithium salts, prenylamine, phenothizine deivatives, chemopreventive drugs including adriamycin.

17. The method according to any of claims 1-5 wherein the condition type is caused by electromagnetic radiation.

18. The method according to any of claims 1-5 wherein condition is caused by an infection infections by protozoa, virus, bacteria, fungus and including AIDS virus, bacterial septicemia, systemic fungal infections, Rickettsial diseases, toxic shock syndrome, infectious mononucleosis, chlamydia thrachomatis, chlamydia psittaci, cytomegalovirus infection, cambylobacter, salmonella, influenza, poliomyelitis, toxoplasmosis, Lassa Fever, Yellow Fever, billharziose, colibacteria, enterococcer, preteus, klebsiella, pseudomonas, staphylococcus aureus, staphylococcus epidermidis, candida albicans, tuberculosis, mumps, infectious mononucleusis, hepatitis and Coxackie virus

19. The method according to any of claims 1-5 wherein the condition is caused by a cancer or a by premalignant disorder having an impact of the heart, including acute leukemia, chronic myelocytic leukemia, chronic lymphocytic leukemia, Hodgkin's disease, lymphosarcoma, myeloma, metastasing carcinoma of any origin.

20. The method according to any of claims 1-5 wherein the condition is caused by any disease selected from diabetis mellitus, conditions with increased fasting levels of LDL-Cholesterol, conditions with combined increased fasting levels of LDL-Cholesterol and tryglycerid, conditions with increased fasting levels of triglycerid, conditions with increased fasting levels of HDL-Cholesterol, retroperitoneal fibrosis, lupus erythematosus, polyarteritis nodosa, sclerodermia, polymyositis, dermatomyositis, rheumatoid arthritis, anaphylaxis, serum sickness, hemolytic anaemia, and allergic agranulocytosis.

21. The method according to any of the preceding claims wherein the condition is selected from ventricular or supra ventricular tachyarrhytmias, atrioventricular block, sinus node disease, Wolff-Parkinson-White syndrome, Lenégres disease, Lev's disease any syndrome involving an abnormal myocardial, connection between atrium and ventricle.

22. The method according to any of the preceding claims wherein the condition is characterised by one or more abnormalities as measured by electrocardiography (ECG).

23. The method according to any of th preceding claims wherein the condition as measured by ECG relates to an alteration selected from one or more changes in the configuration selected from the P wave, the ST segment, the T wave, the QRS complex, the Q wave, the delta wave, and the U wave.

24. The method according to any of the preceding claims wherein the dose of α-MSH and/or of an α-MSH equivalent or a EPO and/or an EPO equivalent or a combination thereof is administered profylactically for preventing a progress of the condition or of any symptom of the condition.

25. The method according to any of the preceding claims wherein the dose of α-MSH and/or of an α-MSH equivalent or an EPO and/or an EPO equivalent or a combination thereof is administered profylactically for preventing the establishment of the condition or of any symptom of the condition.

26. The method according to any of the preceding claims wherein the dose of α-MSH and/or of an α-MSH equivalent or a EPO and/or an EPO equivalent or a combination thereof is administered as a single dosage, regular or continued administration, or as a sequential administration.

27. The method according to any of the preceding claims wherein the tissue comprises one or more cell types selected from macrophages, the reticulo endothelial system monocytes, neutrophil granulocytes, eosinophil granulocytes, basophil granulocytes, T-cells, B-cells, mast cells, and dendritic cells.

28. The method according to claim 27 wherein the cell type is selected from T-cells, B-cells, and mast cells.

29. The method according to any of the preceding claims wherein the administration is selected from parenteral adminstration, including intraperitoneal administration, intrathecal administration systemic administration, local administration, topical administration, transmucosal administration and transdermal administration and oral administration.

30. The method according to any of the preceding claims wherein the administration is selected from systemic administration; injection into tissue or into a body cavity including joints; implantation into tissue or into a body cavity; topical application to the skin or to any gastrointestinal surface, or to a mucosal surface including the lining of body cavities.

31. The method according to any of the preceding claims wherein the α-MSH equivalent is a substance acting on the α-MSH receptor and/or on the melanocortin receptor such as subtypes 1 to 5 (MC-receptors 1-5).

32. The method according to any of the preceding claims wherein the α-MSH equivalent is a polypeptide having at least 3 amino acids including the following sequence Lys-Pro-Val, such as Gly-Lys-Pro-Val, or the following sequence His-Phe-Arg,

33. The method according to claim 32 wherein the combination of α-MSH or α-MSH equivalent with EPO and/or an EPO equivalent has an additive effect.

34. The method according to claim 32 wherein the combination of α-MSH or α-MSH equivalent with EPO and/or an EPO equivalent has a synergistic effect.

35. Use of α-MSH and/or a equivalent of α-MSH or of a EPO and/or an EPO equivalent or a combination of α-MSH and/or of an α-MSH equivalent with a EPO and/or an EPO equivalent for the preparation of a medicament for treatment or prevention according to any of the methods as mentioned in claims 1-34.

36. Use according to claim 35 for the preparation of a medicament for injection or systemic administration, such as a medicament in a form suitable for injection or systemic administration, e.g. a solution or a suspension.

37. Use according to claim 35 for the preparation of a medicament for implantation, characterised in that the medicament is incorporated into a coating of a medico technical device or is incorporated into the material of the device itself, including artificial heart valves and stents.

38. Use according to claim 35 for the preparation of a medicament for topical application in the form of a powder, paste, ointment, lotion, gel, cream, emulsion, solution, suspension, spray, aerosol, sponge, strip, plaster, or pad.

39. Use according to claim 35 for the preparation of a medicament for oral administration in the form of tablets, sustained release tablets, or resoritablets.

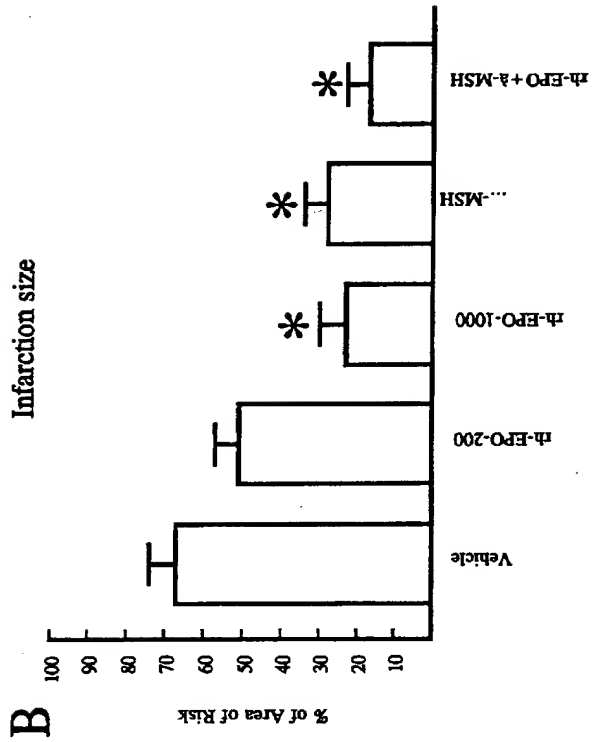
40. Use according to claim 35 for the preparation of a medicament for topical application in the form of a preparation suitable for application on mucosa e.g. a suppository, a tampon, a suspension for irrigation, a tablet or troche, a cream or gel or ointment; or for application on urethral mucosa, a bladder insert, or an implant.

41. Use according to any of claims 35-40 wherein the α-MSH and/or α-MSH equivalent or EPO and/or an EPO equivalent or the combination thereof is present in the medicament in an amount of 0.001-99%, typically 0.01-75%, more typically 0.1-20%, especially 1-10% by weight of the medicament.

42. A pharmaceutical composition comprising a combination of α-MSH or and/or α-MSH equivalent and EPO and/or an EPO equivalent together with a pharmaceutically acceptable carrier.

43. The pharmaceutical composition according to claim 42 wherein the α-MSH or α-MSH equivalent and EPO and/or an EPO equivalent is a physical entity.

44. The pharmaceutical composition according to any of claims 42 and 43 in a form as described in any of the uses of claims 35-41.



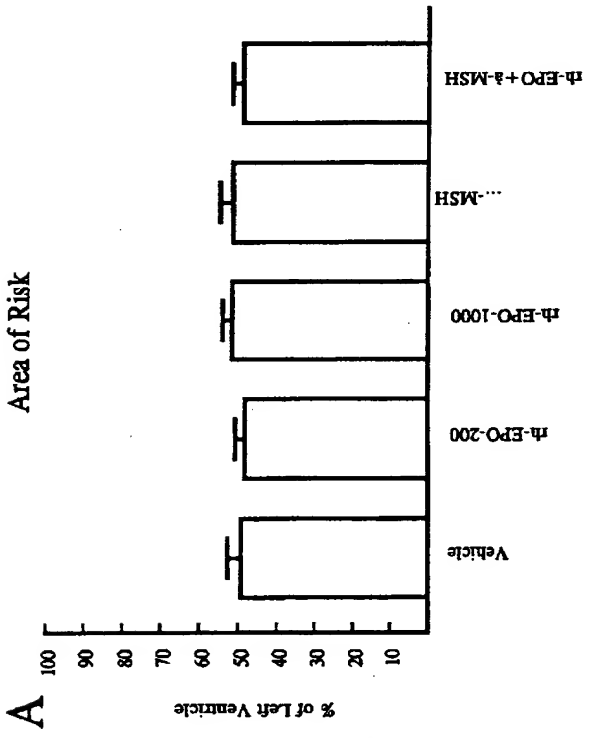


Figure 1

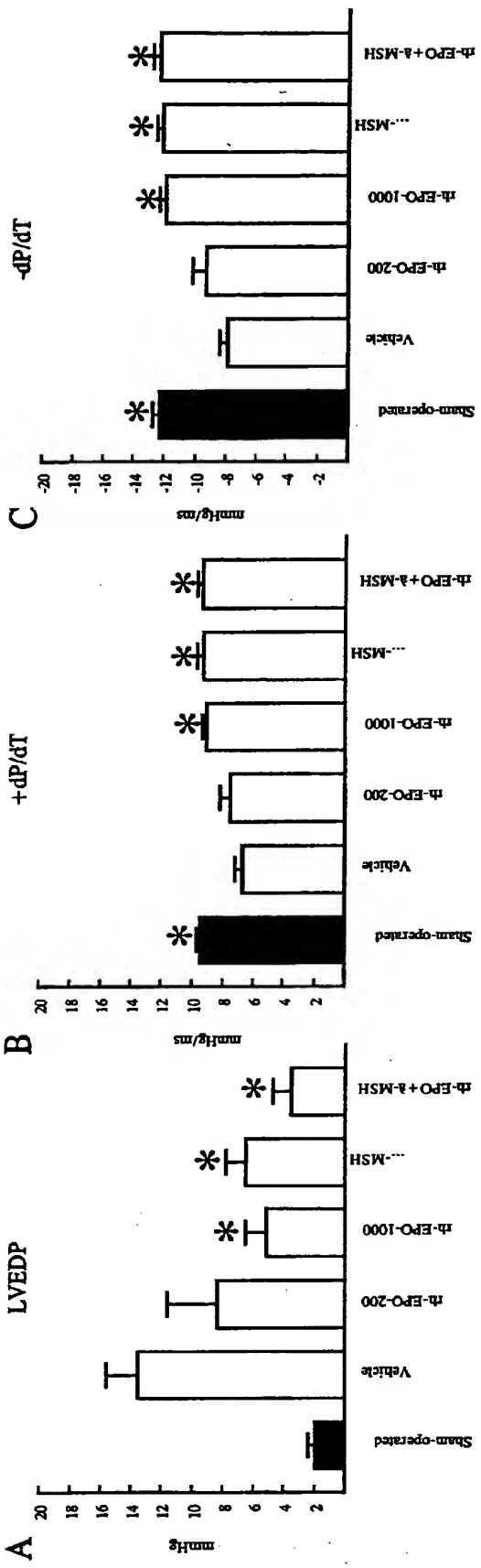


Figure 2